

**COMMITTEE OF EXPERTS ON THE TRANSPORT OF
DANGEROUS GOODS AND ON THE GLOBALLY
HARMONIZED SYSTEM OF CLASSIFICATION
AND LABELLING OF CHEMICALS**

Sub-Committee of Experts on the Globally
Harmonized System of Classification
and Labelling of Chemicals

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**UPDATING OF THE SECOND REVISED EDITION OF THE GLOBALLY HARMONIZED
SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)**

Health hazards

Section 3.4.2 of Chapter 3.4

(refer to documents ST/SG/AC.10/C.4/2008/18 and -2008/18/Add.1)

Note by the secretariat

This document contains the text of section 3.4.2 of Chapter 3.4 as amended by ST/SG/AC.10/C.4/2008/18 and rearranged as proposed in ST/SG/AC.10/C.4/2008/18/Add.1, Annex II.

The corrections and additional amendments to section 3.4.2, proposed in ST/SG/AC.10/C.4/2008/18/Add.1 are shown in visible mode, between square brackets.

“3.4.2 Classification criteria for substances**3.4.2.1 Respiratory sensitizers****3.4.2.1.1 Hazard categories**

3.4.2.1.1.1 Respiratory sensitizers shall be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

3.4.2.1.1.2 Where data are sufficient and where required by a competent authority, a refined evaluation [\[according to 3.4.2.1.1.3\]](#) allows the allocation of respiratory sensitizers into sub-category 1A, strong sensitizers, or sub-category 1B for other respiratory sensitizers.

3.4.2.1.1.3 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitizers. Substances are allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in [\[figure-Table 3.4.1\]](#) and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.

[\[TableFigure 3.4.1\]: Hazard category and sub-categories for respiratory sensitizers](#)

CATEGORY 1:	Respiratory sensitizer
	<p>A substance is classified as a respiratory sensitizer:</p> <ul style="list-style-type: none"> - if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or - if there are positive results from an appropriate animal test².
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests ² . Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests ² . Severity of reaction may also be considered.

3.4.2.1.2 Human evidence

3.4.2.1.2.1 Evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

² At present recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

3.4.2.1.2.2 When considering the human evidence, it is necessary for a decision on classification to take into account, in addition to the evidence from the cases:

- (a) the size of the population exposed;
- (b) the extent of exposure.

3.4.2.1.2.3 The evidence referred to above could be:

- (a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:
 - (i) *in vivo* immunological test (e.g. skin prick test);
 - (ii) *in vitro* immunological test (e.g. serological analysis);
 - (iii) studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects;
 - (iv) a chemical structure related to substances known to cause respiratory hypersensitivity;
- (b) data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

3.4.2.1.2.4 Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

3.4.2.1.2.5 The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognized that in practice many of the examinations listed above will already have been carried out.

3.4.2.1.3 *Animal studies*

Data from appropriate animal studies² which may be indicative of the potential of a substance to cause sensitization by inhalation in humans³ may include:

- (a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice;
- (b) specific pulmonary responses in guinea pigs.

² At present recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

³ The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitizers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyperreactivity, they should not be considered as respiratory sensitizers.

3.4.2.2 *Skin sensitizers*

3.4.2.2.1 *Hazard categories*

3.4.2.2.1.1 Skin sensitizers shall be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

3.4.2.2.1.2 Where data are sufficient and where required by a competent authority, a refined evaluation according to 3.4.2.2.1.3 allows the allocation of skin sensitizers into sub-category 1A, strong sensitizers, or sub-category 1B for other skin sensitizers.

3.4.2.2.1.3 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitizers as described in [3.4.2.2.24]. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in [figureTable 3.4.2](#) and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values provided in [3.4.2.2.1.42.1 and 3.4.2.2.3.2] for sub-category 1A and in [3.4.2.2.1.2.25 and 3.4.2.2.3.3] for sub-category 1B.

[TableFigure 3.4.2]: Hazard category and sub-categories for skin sensitizers

CATEGORY 1:	Skin sensitizer
	<p>A substance is classified as a skin sensitizer</p> <ul style="list-style-type: none"> - if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or - if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

[\[3.4.2.2.1.42 Human evidence \]](#)

[\[3.4.2.2.2.1\]](#) Human evidence for sub-category 1A can include:

- positive responses at $\leq 500 \mu\text{g}/\text{cm}^2$ (HRIPT, HMT – induction threshold);
- diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;
- other ~~epidemiology~~ **epidemiological** evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

[3.4.2.2.1.52.2] Human evidence for sub-category 1B can include:

- (a) positive responses at $> 500 \mu\text{g}/\text{cm}^2$ (HRIPT, HMT – induction threshold);
- (b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;
- (c) other ~~epidemiology~~ **epidemiological** evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

[3.4.2.2.43] *Animal studies*

[3.4.2.2.43.1] For Category 1, when an adjuvant type test method for skin sensitization is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant Guinea pig test method a response of at least 15% of the animals is considered positive. For Category 1, a stimulation index of 3 or more is considered a positive response in the Local Lymph Node Assay. Test methods for skin sensitization are described in the OECD Guideline 406 (the Guinea Pig Maximisation test and the Buehler guinea pig test) and Guideline 429 (Local Lymph Node Assay). Other methods may be used provided that they are well-validated and scientific justification is given. The Mouse Ear Swelling Test (MEST), appears to be a reliable screening test to detect moderate to strong sensitizers, and can be used as a first stage in the assessment of skin sensitization potential.

[3.4.2.2.3.2] Animal test results for sub-category 1A can include data with values indicated in [Table 3.4.13] below:

[Table 3.4.13]: Animal test results for sub-category 1A

Assay	Criteria
Local lymph node assay	EC3 value $\leq 2\%$
Guinea pig maximisation test	$\geq 30\%$ responding at $\leq 0.1\%$ intradermal induction dose <u>or</u> $\geq 60\%$ responding at $> 0.1\%$ to $\leq 1\%$ intradermal induction dose
Buehler assay	$\geq 15\%$ responding at $\leq 0.2\%$ topical induction dose <u>or</u> $\geq 60\%$ responding at $> 0.2\%$ to $\leq 20\%$ topical induction dose

[3.4.2.2.3.3] Animal test results for sub-category 1B can include data with values indicated in [Table 3.4.24] below:

Table [3.4.24]: Animal test results for sub-category 1B

Assay	Criteria
Local lymph node assay	EC3 value $> 2\%$
Guinea pig maximisation test	$\geq 30\%$ to $< 60\%$ responding at $> 0.1\%$ to $\leq 1\%$ intradermal induction dose <u>or</u> $\geq 30\%$ responding at $> 1\%$ intradermal induction dose
Buehler assay	$\geq 15\%$ to $< 60\%$ responding at $> 0.2\%$ to $\leq 20\%$ topical induction dose <u>or</u> $\geq 15\%$ responding at $> 20\%$ topical induction dose”

| [3.4.2.2.24] *Specific considerations*

| [3.4.2.2.24.1] For classification of a substance, evidence should include any or all of the following, using a weight of evidence approach:

- (a) Positive data from patch testing, normally obtained in more than one dermatology clinic;
- (b) Epidemiological studies showing allergic contact dermatitis caused by the substance; Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;
- (c) Positive data from appropriate animal studies;
- (d) Positive data from experimental studies in man (see Chapter 1.3, para. 1.3.2.4.7);
- (e) Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic;
- (f) Severity of reaction may also be considered

| [3.4.2.2.24.2] Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on ~~contact~~ [skin] sensitization are usually derived from case-control or other, less defined studies. Evaluation of human data must therefore be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies. For both animal and human data, consideration should be given to the impact of vehicle.

| [3.4.2.2.24.3] If none of the above mentioned conditions are met, the substance need not be classified as a skin sensitizer. However, a combination of two or more indicators of skin sensitization as listed below may alter the decision. This shall be considered on a case-by-case basis.

- (a) Isolated episodes of allergic contact dermatitis;
- (b) Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;
- (c) Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in [3.4.2.2.43.1], but which are sufficiently close to the limit to be considered significant;

- (d) Positive data from non-standard methods;
- (e) Positive results from close structural analogues.

[3.4.2.2.34.4] *Immunological contact urticaria*

Substances meeting the criteria for classification as respiratory sensitizers may in addition cause immunological contact urticaria. Consideration should be given to classifying these substances also as skin sensitizers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitizers should also be considered for classification as skin sensitizers.

There is no recognized animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be based on human evidence which will be similar to that for skin sensitization.”
